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09/465,925	12/17/1999	JOHN J. ROSSI	2124-314	9504

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EXAMINER

SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 07/16/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Fig

## Office Action Summary

Application No.

09/465,925

Applicant(s)

ROSSI ET AL.

Examiner

J. Douglas Schultz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 01 May 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3-5,8 and 9 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-5,8 and 9 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

***Response to Arguments***

1. In view of the appeal brief filed on May 1, 2003, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

2. Appellants' appeal brief filed May 1, 2003 has been considered. Rejections and/or objections not reiterated from the Final Rejection mailed May 2, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

***Drawings/Specification***

3. The drawings are objected to because figure 4 is missing. If applicant intends to omit figure 4, the remaining figures and legends should be renumbered so that no gap exists in their numbering. A proposed drawing correction or corrected drawings are required in reply to the

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Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

*Response to Arguments*

4. Claims 1, 3-5, 8, and 9 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to a method of colocalizing an inhibitory agent comprising a localization signal in cells *in vitro*, does not reasonably provide enablement for a method of colocalizing an inhibitory agent comprising a localization signal in cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is maintained for the same reasons of record as cited in the rejection mailed May 2, 2002.

Applicants have argued that no basis has been provided for doubting that the methods taught in the specification have applicability for in *in vivo* use, that the specification discloses a number of methods, presumably supporting *in vivo* use, including viral-mediated delivery, and that the level of skill in the art is high. Applicants conclude that there is no evidence that the instantly contemplated delivery system would not work *in vivo*.

These arguments are not considered convincing. While applicants correctly point out that they have disclosed a number of methods, they fail to note that such methods are only prophetically disclosed as they pertain to *in vivo* use. While exemplification *in vivo* has never been required by the Office in support of enablement, applicants have provided actual results only from *in vitro* studies, which are not considered analogous to an *in vivo* model system for

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reasons provided in earlier office actions. Such evidence demonstrates that one cannot use results obtained *in vitro* to predict what will happen *in vivo*, due to unique issues related to *in vivo* use of nucleic acid therapeutics, such as cellular and target access, and immune and non-specific interactions that cannot be tested for *in vitro*. One of skill in the art would readily recognize, particularly in light of the multiple cited references, that contrary to applicants unsupported contention, the level of skill in using nucleic acid based therapeutics *in vivo* is not high, and that one cannot move predictably from results obtained *in vitro* to methods of target inhibition *in vivo*.

Applicants have not provided any support for their allegation that “the state of the art is obviously quite high”, which is notable considering that such “obvious” evidence should also be easy to find. To the contrary, applicants contend that no evidence has been provided to doubt that applicants claimed methods would work *in vivo*. However, in order to reach this conclusion, applicants would have to had ignored multiple citations from three review articles that explicitly discuss the difficulties of the *in vivo* use of nucleic acid based therapeutics. Applicants argue that the references actually support applicants claims of enablement, and alternatively that the Office placed an unwarranted level of importance on them. While applicants concede that “each article does discuss the difficulties inherent in the field”, applicants argue that such problems are not insurmountable. Applicants point to Gewirtz et al., who states that several nucleic acid based therapeutics have reached clinical trials, and to Branch, who report that there is growing evidence that antisense molecules can be useful pharmacological tools when applied carefully.

In response, it is set forth that the “difficulties inherent in the field” still remain, and although isolated instances of *in vivo* nucleic acid-mediated inhibition have been shown, it is the

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unpredictability of basing a prediction of *in vivo* success based on *in vitro* results that is at issue.

Even the isolated instances of success have been called into question. For example, applicants are directed to Branch (page 46, cols. 2 and 3), wherein it is indicated that in some of these studies, poor design has led to lax standards, and that an informal poll by a recognized scientist in the field indicated that the accuracy of published papers ranges from 5% to 50% being accurate.

Furthermore, regarding applicants' citation of Gewirtz et al. that several nucleic acid based therapeutics have reached clinical trials, a recent news (Reuters, March 17, 2003) is enclosed that describes yet another failed clinical trial using nucleic acid based therapeutics, and shows that even today, 3.5 years after applicants' instant filing date, and 9.5 years after applicants' earliest priority date, only one nucleic acid based therapeutic has ever received FDA approval, and that even here, the drug is injected directly into the eye, which bypasses issues of cellular access and mal-adaptive immune responses. According to the Reuter's article, "Isis currently makes the world's only commercial antisense drug-- a treatment for a rare type of eye infection in AIDS patients." Thus even this one drug is not representative of any nucleic acid based therapeutic as instantly claimed. It is important to note that no other drugs referenced by Gewirtz et al. have been found to have any efficacy, because had the nucleic acid based drugs in clinical trials referenced by Gewirtz (published in 1996) actually worked, the Reuter's article would not have indicated in 2003 that only one drug been FDA approved. Finally, the Reuters' article concludes that "Many once promising antisense drugs have failed, including experimental therapies from Isis for HIV and genital warts."

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These review articles, whose sole purpose is to summarize the state of the art, identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins. The fact that their publication date occurs after applicants' earliest priority date underscores how persistent these fundamental problems are. Contrary to applicants' assertion, the post-filing citations do not run afoul of M.P.E.P. §2164.05(a); applicants' citation of this passage must be put in its proper context. Picking up from the sentence following applicants' M.P.E.P. citation:

"Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered.

The articles cited discuss only those difficulties that had and continue to be longstanding obstacles opposing enablement, and are thus appropriate. For example, in discussing the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Branch states that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

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The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, “[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency” (Page 378). “[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations.” (Page 379).

In discussing the non-specific toxicity effects of *in vivo* antisense administration; Branch affirms that “non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis” (Page 50), Further, Branch reasons that “the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available” (Page 46, second column).

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the *in vitro* inhibition of protein expression as being correlative or representative of the successful *in vivo* use of such nucleic acid compounds. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of nucleic acid therapeutics in inhibiting a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the demonstrated unpredictability in

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the art associated with appropriate *in vivo* delivery provided by nucleic acid based therapeutics, and specifically regarding the instant methods claimed.

Said claims are drawn very broadly to methods of inhibiting targets in cells both *in vitro* and *in vivo*. Since the specification fails to provide any guidance for the successful *in vivo* use of such compounds, and since resolution of the various complications in regards to targeting a particular gene in an organism is unpredictable as demonstrated in the cited references, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and /or tissues. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

5. Claims 1, 3-5, 8, and 9 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 5,827,935, for the same reasons of record as set forth in the Office action mailed January 8, 2001. Applicants have indicated that they will submit a terminal disclaimer upon indication of allowable subject matter.

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*Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, and by dependency 3-5, 8, and 9 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step related to positioning. The term “positioning” may be interpreted as either a noun, in which case it would not comprise an active step, or alternatively as a verb, which therefore comprises an active step. Because the claim later references “said positioning being such that the concentration of the inhibitor molecule with respect to the target molecule is enhanced”, which denotes the term “positioning” as a gerund and therefore a noun, such language is not considered an active step. Correction is required; however, strictly for the purpose of advancing prosecution, and since the claim comprises no other active steps, the term “positioning” is interpreted as an active step. Applicants’ correction is required.

7. Claims 1 and by dependency, claims 3-5, 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a process comprising co-localizing a target mRNA and a ribozyme inhibitor of said target.

It is not clear from this description whether the “ribozyme inhibitor” refers to the ribozyme itself as an inhibitory molecule, or alternatively, to an inhibitor of said ribozyme. Although the claim language reciting a “ribozyme inhibitor for said target molecule”, suggests

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that it is the ribozyme itself that is the inhibitor, the claim language should clearly set forth the compounds being claimed. It is assumed for the remainder of the Office action that the claim refers to the ribozyme as an inhibitor. However, clarification is required.

8. Claim 8, step (iii) recites the limitation "a 3' untranslated region (UTR) of said RNA molecule". The claim references both a RNA target molecule, and a tRNA<sub>3</sub><sup>Lys</sup> molecule, but no "RNA molecule" *per se*. Thus, there is insufficient antecedent basis for the reference to "said RNA molecule" in the claim.

#### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claim 5 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 5 is drawn to a living cell in which a RNA target molecule and a ribozyme inhibitor for said target molecule are co-localized.

The claim as filed reads on a human, which is non-statutory subject matter. Furthermore, the claim as filed does not show the hand of man, since the cell is not indicated as being isolated from its natural state.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, and 3-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Sarver et al. (Science 1990. 247:1222-1225).

The invention of the above claims is drawn to a process comprising the positioning within a living cell an RNA target molecule and a ribozyme inhibitor for said target molecule, said positioning being such that the concentration of the inhibitor molecule with respect to the target molecule is enhanced, wherein said target RNA is an HIV-1 RNA and the ribozyme inhibitor cleaves an HIV-1 molecule, or a method of co-localizing a ribozyme and its target in living cell, or the living cell that comprises a ribozyme and a target.

Sarver et al. teaches an HIV-1 specific ribozyme and its transfection into a living cell, thereby meeting all the limitations of the above claims.

11. Claims 1, 3-5, 8, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Bueg et al. (U.S. Patent Number 5,354,844).

The claims above are drawn to a process comprising the positioning within a living cell an RNA target molecule and a ribozyme inhibitor for said target molecule, said positioning being such that the concentration of the inhibitor molecule with respect to the target molecule is enhanced, wherein said target RNA is an HIV-1 RNA and the ribozyme inhibitor cleaves an HIV-1 molecule, or a method of co-localizing a ribozyme and its target in living cell, or the living cell that comprises a ribozyme and a target, or a method comprising co-localizing a target mRNA and a ribozyme that cleaves said target, wherein the ribozyme further comprises a

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dimerization or packaging signal of the target, or comprises a sequence capable of pairing with said RNA target molecule such that the ribozyme contains a tRNA<sub>3</sub><sup>Lys</sup> molecule at the 3' end of said tRNA molecule and binds upstream of a tRNA<sub>3</sub><sup>Lys</sup> binding site of the target RNA molecule, or wherein the ribozyme contains a sequence capable of binding to a protein to which the target RNA also binds, wherein said protein may be multimeric, wherein said target mRNA is an HIV-1 RNA molecule.

Beug et al., at col. 8, lines 3-13, teach a method of inserting a ribozyme into a tRNA gene such that when the tRNA gene is transcribed, the ribozyme becomes part of the transcription unit. Thus the disclosure of Beug et al. meets the instant limitations whereby a ribozyme contains a sequence that causes it to bind to a protein that the target transcript will bind to. Later on line 20 of the same column, Beug indicates that such compositions may be used to fight pathogens such as HIV.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

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evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 3-5, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sarver et al. (above) in view of Beug et al. (above), Sullenger et al. (of record) and Weiss et al.

The claims above are drawn to a process comprising the positioning within a living cell an RNA target molecule and a ribozyme inhibitor for said target molecule, said positioning being such that the concentration of the inhibitor molecule with respect to the target molecule is enhanced, wherein said target RNA is an HIV-1 RNA and the ribozyme inhibitor cleaves an HIV-1 molecule, or a method of co-localizing a ribozyme and its target in living cell, or the living cell that comprises a ribozyme and a target, or a method comprising co-localizing a target mRNA and a ribozyme that cleaves said target, wherein the ribozyme further comprises a dimerization or packaging signal of the target, or comprises a sequence capable of pairing with said RNA target molecule such that the ribozyme contains a tRNA<sub>3</sub><sup>Lys</sup> molecule at the 3' end of said tRNA molecule and binds upstream of a tRNA<sub>3</sub><sup>Lys</sup> binding site of the target RNA molecule, or wherein the ribozyme contains a sequence capable of binding to a protein to which the target RNA also binds, wherein said protein may be multimeric, wherein said target mRNA is an HIV-1 RNA molecule.

The teachings of Sarver are relied upon as described above.

Sarver et al. do not teach an HIV-1 specific ribozyme conjugated to sequences comprising packaging signals or sequences that bind to proteins capable of binding the target.

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Beug et al., at col. 8, lines 3-13, teach a method of inserting a ribozyme into a tRNA gene such that when the tRNA gene is transcribed, the ribozyme becomes part of the transcription unit. Thus the disclosure of Beug et al. meets the instant limitations whereby a ribozyme contains a sequence that causes it to bind to a protein that the target transcript will bind to. On line 20 of the same column, Beug indicates that such compositions may be used to fight pathogens such as HIV.

Sullenger et al. teach conjugating antisense nucleic acids to tRNA, wherein the conjugate is capable of binding a protein that the target mRNA also binds to.

Barat et al. teaches that tRNA<sub>3</sub><sup>Lys</sup> interacts with HIV-1 reverse transcriptase and serves as a specific primer for retroviral incorporation of DNA into the host genome.

It would have been obvious to one of ordinary skill in the art to make and use HIV-1 specific ribozymes that are conjugated to a tRNA<sub>3</sub><sup>Lys</sup>, or to sequences that bind a protein that a target RNA transcript also binds to, since the HIV-1 specific ribozymes were taught by Sarver, ribozymes conjugated to a tRNA gene were taught by Beug et al., HIV-1 targeted antisense-tRNA conjugates were taught by Sullenger et al., and since Barat teach that tRNA<sub>3</sub><sup>Lys</sup> is a specific primer for HIV-1 reverse transcription. One would have been motivated to make ribozyme-tRNA<sub>3</sub><sup>Lys</sup> conjugates because Barat et al. teaches that tRNA<sub>3</sub><sup>Lys</sup> preferentially binds to HIV-1 reverse transcriptase, and since both Sullenger and Beug teach methods of targeting tRNA-conjugated nucleic acid inhibitors (antisense and ribozymes, respectively) that bind to HIV-1 targets, such as HIV reverse transcriptase. Finally, one of ordinary skill in the art would have had a reasonable expectation of success in making such tRNA-ribozyme constructs, because Sullenger teaches how to conjugate tRNA to antisense molecules, which, like

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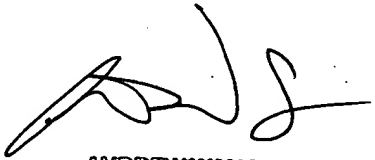
ribozymes, are nucleic acid oligos. Therefore, in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD  
July 7, 2003



ANDREW WANG  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600